UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,520	07/20/2001	Barbara L. Hempstead	19603/2595	9715

7590 01/21/2004

Michael L Goldman
Nixon Peabody
Clinton Square
PO Box 31051
Rochester, NY 14603

EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,520	HEMPSTEAD ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,10,14-16,18,19 and 55-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,10,14-16,18,19 and 55-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *41403* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Request for Continued Examination

Re: Hempstead *et al.*

Date of priority: September 28, 1998

The request filed on 10-22-03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/830520 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 7, 9-10, 14-16, 18-19, and 55-60 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 04-14-03 has been considered by the examiner. A signed copy of the 1449 is attached.

Rejections Maintained:

Claims 7, 9-10, 14-16, 18-19, and 55 remain rejected and new Claims 56-60 are rejected under 35 U.S.C. 102(e) as being anticipated by Alps *et al.* (US Patent No. 5,733,871, March 1995) for the reasons of record.

Alps *et al.* teaches as set forth previously in the Action mailed 12-20-2002. Applicant's amendments do not substantially alter the scope of the claims to merit removal of the rejections with regards to inherency. Applicants argue (Remarks 10/22/03; page 4) that the Alps reference "relates" to the treatment of neuronal damage in the CNS of individuals in need of such treatment. True, Alps *et al.* teach the intravenous administration of the claimed trk receptor ligands for the purposes of treating neuronal damage in the central nervous system of individuals in need of such treatment (abstract, column 3, lines 58+). However, the prior art further identifies the population of patients that the trk receptor ligands intend to treat: those who have suffered a stroke or cardiac arrest which results in ischemic or hypoxic damage (column 4, lines 55+). This patient population has not been distinguished from those who are suffering from the claimed methods of treating persons with "cardiac ischemia", those who are suffering from a "vascular disorder"; and those who are suffering from a "non-cardiac vascular disorder". Furthermore, the specification defines (page 17) cardiac ischemia as including *cerebrovascular* disorders caused by insufficient cerebral circulation. The specification further includes "strokes" as a non-cardiac vascular disorder. Thus, as set forth previously, the prior art teaches the administration of the claimed compounds to the same population of patients as claimed, with the same route of delivery as claimed and inherently such compounds would induce angiogenesis in the treated patients. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562

F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

New Rejection:

Claims 7, 9-10, 14-16, 18-19, 55-60 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing angiogenesis in a patient that has cardiac ischemia or a vascular disorder comprising administering to the patient an angiogenesis-inducing effective amount of BDNF, NT-3, or NT-4, does not reasonably provide enablement for administering any and all trk receptor ligands, trk B receptor ligands, or trk C receptor ligands, or recombinant and small molecule mimics of BDNF, NT-3 or NT-4 that interact with and activate trk receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to broadly drawn to methods of inducing angiogenesis in a patient that has cardiac ischemia, or any vascular disorder including a non-cardiac vascular disorder, comprising administering trk receptor ligands .

The specification teaches (page 11) that trk ligands include proteins or polypeptides and fragments thereof, including the native neurotrophins and mutants thereof, small chemical molecules, recombinant molecules, and chimeric molecules which interact with and activate trk receptors. The specification further teaches that chimeric trk receptor ligands include mutagenized neurotrophins which are capable of activating more than one trk receptor .

Thus, based on the teaching of the specification, the claims include methods of inducing angiogenesis in certains patients comprising administering a whole universe of molecules that may be considered trk ligands.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any and all molecules that may bind trk receptors with or without the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified molecules and or proteins because it has not been shown that these modified compounds are capable of functioning as that which is being disclosed.

With regards to protein derivatives, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological

activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed ligands can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that any and all molecules that bind to trk receptors will predictably function as disclosed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at 571-272-0871. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
January 16, 2004